Chapter 3

CARDIOVASCULAR SYSTEM

Table of Contents

	Page
Introduction	47
A. Angina Pectoris	49
1. Exercise Performance	49
a. Intensity of reduction of exercise performance	50
b. Carboxyhemoglobin levels of anginal patients	51
c. Heart rate effects of inhalation of carbon monoxide	53
d. Heart rate effects of cigarette smoking	54
e. Coronary blood flow and myocardial metabolism	54
2. Electrocardiogram as a Sign of Myocardial Oxygenation	55
a. Precipitation of angina pectoris by cigarette smoking	55
b. Electrocardiogram of non-anginal subjects	56
3. Coronary Arteriography	57
4. Does Carbon Monoxide Provoke Angina Pectoris?	58
B. Myocardial Infarction	60
1. Association Between Atherosclerotic Disease and Carbon Monoxide Exposure	60
2. Association Between Carboxyhemoglobin Levels and Myocardial Infarction	62
a. Retrospective studies of myocardial infarction deaths.	63
b. Prospective studies of patients with myocardial infarction	64
3. What is the Significance of Carboxyhemoglobin Levels in Patients with Myocardial Infarction?	66
C. Cardiac Effects of Carbon Monoxide, Nicotine and Cigarette Smoke	68
1. Carbon Monoxide	69
2. Nicotine	70
a. Myocardial contractility and cardiac output	70
b. Coronary circulation	71
3. Cigarette Smoke	72
D. Experimental Atherosclerosis	73
1. Rabbits	74
2. Mice, Rats, Hamsters and Dogs	76
3. Subhuman Primates	77
4. Human Subjects	79
E. Design of Future Experiments	79
Bibliography	81

1005105285

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

In recent years, there has been a considerable amount of attention directed at the cardiovascular effects of carbon monoxide in general and in particular to that inhaled while cigarette smoking. The two-hundred articles cited in this chapter are those that relate to this subject. However, only about 10% of these articles relate directly to carbon monoxide in cigarette smoke. The remainder of the articles are on the effects of carbon monoxide without the components of cigarette smoke.

The cardiovascular effects of carbon monoxide have, therefore, been examined as a single chemical, usually administered in concentrations much higher than those experienced in the course of cigarette smoking. The inhalation of lethal quantities of carbon monoxide causes cardiac arrest. The highest concentration that does not exert toxicity on the heart has been difficult to ascertain since various experiments in several animal species have resulted in varying threshold limits. The least conservative estimate states that the carbon monoxide contained in cigarette smoke is harmful to the heart of the smoker. This is the opinion of four groups of scientists and is discussed in the sections below. (a) Aronow, who claims that carbon monoxide aggravates coronary heart disease; (b) Wald, who describes a correlation between carboxyhemoglobin level and the incidence of arterial disease; (c) Ayres, who noted a depression of cardiac function in the experimental heart preparation perfused with blood containing high levels of carboxyhemoglobin; and (d) Astrup and Kjeldsen, who have identified arteriosclerotic lesions in rabbits fed with cholesterol and exposed to carbon monoxide.

1005105286

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

The four conclusions taken as a group have convinced some authorities to subscribe to the proposition that carbon monoxide contained in cigarette smoke causes cardiac disease, specifically angina pectoris and myocardial infarction. These authorities have overlooked the fundamental feature of most of their experimental observations as stated above, i.e. they used carbon monoxide inhalation, a procedure that does not relate directly to cigarette smoke. Furthermore, there has been no confirmation of the four concepts and there are even conflicting results which question the validity of the experimental evidence supplied by the four investigators mentioned above.

1005105287

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

A. Angina Pectoris

The most frequently-cited evidence that carbon monoxide contained in cigarette smoke is harmful to the heart is the series of experiments conducted by Aronow et al. Since 1969, they have been studying patients with angina pectoris on maximal treadmill exercise.[1-14] The patients inhaled smoke from cigarettes of varying nicotine content, as well as carbon monoxide administered as a mixture from a compressed air tank or by exposing the patient in a freeway.

In recent review articles,[15-22] Aronow has concluded that "nicotine and carbon monoxide both aggravate angina pectoris and contribute to increased incidence of fatal and nonfatal myocardial infarction and sudden death from coronary heart disease in cigarette smokers."[19] Aronow based his conclusion relating to myocardial infarction and sudden deaths on observations by selected investigators, ignoring the conflicting results of others (see B). Aronow's own studies on aggravation of angina pectoris have not been confirmed. This section reviews the contradictions to Aronow's conclusion that "nicotine and carbon monoxide both aggravate angina pectoris."

1. Exercise Performance.

The basic test used by Aronow et al. measures the duration of time that a subject can tolerate exercise on a treadmill. The endpoint of the procedure

10510528

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

is a subjective one, i.e. chest pains, and has been criticized by Theodore,[23] Garfein and Dwyer[24] and Lescoe.[25] The last-mentioned cardiologist cited Aronow's own remarks to a newspaper reporter that the subjective exercise performance test can be improved in half of his patients receiving a placebo. There are serious inconsistencies in the results of Aronow's experiments which are as follows:

a. Intensity of reduction of exercise performance. An examination of the results of Aronow et al. indicates the following changes in exercise performance as a result of exposing anginal patients to carbon monoxide or cigarette smoke:

(No. of patients) procedure	Exercise time in sec. ± SD control	exposure	Δ
(10) breathing freeway air[7]	249 ± 82	174 ± 87	75
(10) 50 ppm carbon monoxide[8]	224 ± 43	187 ± 36	37
(10) marihuana cigarette[12]	244 ± 16	129 ± 13	115
(10) high-nicotine cigarettes[14]	241 ± 51	185 ± 43	56

When the results of four publications appearing from 1972 to 1975 are examined as a group, the most surprising feature is the consistency of mean control exercise time from 224 to 249 sec. The publications do not state whether the same ten patients were used from study to study. In any event, the smoking of a high-nicotine cigarette caused a shortening of mean exercise time by 56 sec, which is slightly higher than the standard deviation (51) of the control values.

There is no confirmation that cigarette smoking reduced the exercise per-

1005105289

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

formance of anginal patients. With low levels of carbon monoxide, Anderson et al.[26] observed no effect of 50 ppm inhalation but shortening of exercise performance after inhalations of 100 ppm. It is significant that Anderson et al did not find a difference in response to carbon monoxide exposure between anginal patients who were smokers and those who were nonsmokers.

Aronow et al.[7,8,12,14] and Anderson et al.[26] are the only investigators who have used the shortening of exercise time to provoke angina pectoris as a sign that low levels of carbon monoxide are harmful to the anginal patient (see next paragraph). It might be argued that the earlier onset of pain may also be desirable because there is an earlier warning to the patient to stop exertion. The stimulus that excites anginal pain has not been identified although there is recent evidence to implicate coronary vasospasm (Kattus[27]). Carbon monoxide and nicotine can be excluded as causative agents because these constituents of cigarette smoke do not constrict the coronaries.

b. Carboxyhemoglobin levels of anginal patients. Another surprising feature of the results of Aronow et al. is the uniform mean arterial blood carboxyhemoglobin levels and low standard deviation from study to study:

number of subjects	COHb % saturation mean ± S. D. arterial blood	venous blood
(10) angina; 3 smokers, 7 nonsmokers[7]		0.83 ± 0.23
(10) angina; all nonsmokers[8]	1.03 ± 0.27	
(10) intermittent claudication; 2 smokers, 8 nonsmokers[9]	1.08 ± 0.24	

1005105290

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

number of subjects	COHb % saturation mean ± S. D. arterial blood	venous blood
(8) angina; all smokers[11]	2.28 ± 0.46	2.16 ± 0.45
(10) angina; all smokers[12]	2.43 ± 0.14	
(10) healthy; all nonsmokers[13]	1.67 ± 0.33	
(10) angina; all smokers[14]	2.19 ± 0.50	

The above results are lower than any previously-reported series of smokers and nonsmokers, both for mean values and for standard deviation (see Chapter 2). In the series of 10 anginal patients reported by Anderson et al.,[26] (the carboxyhemoglobin values for 5 smokers and 5 nonsmokers) the standard deviation was 0.6 whereas, a similar mixed group reported by Aronow et al.[7] had a standard deviation of 0.23.

There is reason to suspect that the analysis of low levels of carboxyhemoglobin performed by Aronow et al. are inaccurate especially when the results of coronary sinus blood analysis are considered together with arterial blood in 8 subjects before and after smoking each of three cigarettes or inhaling 150 ppm carbon monoxide:[11]

Procedure on 8 angina patients	arterial mean ± S. D.	venous mean ± S. D.	Δ mean
control	2.16 ± 0.45	2.24 ± 0.39	-0.08
after 1 cigarette	3.15 ± 0.51	2.81 ± 0.50	+0.34
after 2 cigarettes	3.76 ± 0.49	3.48 ± 0.53	-0.28
30 min after 2 cigarettes	3.25 ± 0.50	3.21 ± 0.50	+0.04
after 3 cigarettes	4.16 ± 0.48	3.90 ± 0.51	+0.26

100510529L

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

Procedure on 8 angina patients	arterial mean ± S. D.	venous mean ± S. D	Δ mean
control	2.05 ± 0.32	2.04 ± 0.35	+0.01
after 150 ppm CO	4.21 ± 0.36	3.86 ± 0.39	+0.35

The above differences between arterial and coronary sinus blood were over looked by Aronow et al. It seems that in the same group of patients, there is either a release (as much as 0.28 vol %) or uptake (as much as 0.35%). Since the heart is not known to produce or metabolize carbon monoxide, the differences reflect an error in the analysis of as much as 0.23 + 0.35%, i.e. 0.63% carboxyhemoglobin. The error of analysis is as large as the standard deviation of the series. The carboxyhemoglobin levels reported by Aronow et al. have never been duplicated by any other cardiologist in respect to the homogenous nature of anginal patients.

c. Heart rate effects of inhalation of carbon monoxide. An analysis of the the effects of inhalation of carbon monoxide reveal the following:

subjects	mean + S. D. beats/min control	after
(10) angina breathing freeway air[7]	80.6 ± 5.0	81.8 ± 6.6
(10) angina breathing 50 ppm CO[8]	74.8 ± 75.0	75.0 ± 5.74
(8) angina breathing 150 ppm CO[11]	72.4 ± 4.7	72 ± 5.5
(10) healthy breathing 100 ppm CO[13]	74.4 ± 7.2	73.4 ± 9.6

1005105292

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

The above results indicate a steady state of inhalation of up to 150 ppm carbon monoxide does not influence the heart rate. Shephard[28] also reported no change in heart rate in subjects inhaling carbon monoxide to increase the carboxyhemoglobin level by 2.4 to 5.4%.

d. Heart rate effects of cigarette smoking. That nicotine caused an acceleration in heart rate was the conclusion of Aronow et al. on the basis of comparing the heart rate response to inhalation of cigarettes with varying amounts of nicotine.[6,10,14] The slight increase in heart rate is accompanied by a small rise in blood pressure but no increase in cardiac index. These observations confirm the earlier results of Regan et al.[29-31] Pentecost and Shillingford[32] and Summers et al.[33] In patients with coronary heart disease, although smoking caused tachycardia, there is no accompanying increase in cardiac output.

e. Coronary blood flow and myocardial metabolism. That cigarette smoking does not reduce coronary blood flow was proven by Bargeron et al.[34] who applied the nitrous oxide technique and catheterization of the coronary sinus. Cigarette smoking in 30 normal subjects caused a significant rise in coronary blood flow, a decline in coronary vascular resistance and myocardial extraction of glucose and oxygen. In 7 males with myocardial infarction, smoking still caused an increase in blood pressure and heart rate. In 3 of the patients, coronary blood flow did not change, while in 3 others, it fell slightly.[29-31] Although there was a slight increase in oxygen consumption in 3 cases, the

1005105293

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

myocardial efficiency was also increased. The data reported illustrate that, in patients with coronary heart disease, smoking results in no reduction of myocardial efficiency. In 15 patients with angiographically-demonstrated severe obstructive coronary artery disease, cigarette smoking did not induce lactate production by the heart.[33] There was no evidence of myocardial ischemia as determined by abnormalities in lactate extraction based on analysis of coronary arterial and sinus blood samples.

2. Electrocardiogram as a Sign of Myocardial Oxygenation.

The electrocardiogram has been used to assess the adequacy of oxygenation of the myocardium. The signs of ischemia include depression of the S-T segment, inversion of the T wave and alteration in the configuration and duration of the QRS complex. In the following paragraphs the influence of smoking on the electrocardiogram is differentiated between anginal patients and healthy individuals not suffering from coronary heart disease.

a. Precipitation of angina pectoris by cigarette smoking. Oram and Sowton[35] sent a questionnaire to 721 patients suffering from angina pectoris. The patients were asked if, in their opinion, smoking had any effect on their chest pains. Of the 309 smokers who responded, 20 experienced angina pectoris shortly after lighting a cigarette.

The 20 patients who considered that their chest pain was precipitated or aggravated by smoking were reexamined clinically and in each case, electrocardiograms were taken, as follows: A resting 12-lead record was first made.

1005105294

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

The electrocardiogram was repeated either after the patient had smoked until pain was induced, or after three cigarettes had been smoked consecutively. A maximum tolerance exercise test was then performed, and at its conclusion, a third record was taken. The patient was, at once, asked to smoke again, and a further record made. After a rest of about 45 minutes, a second maximum-tolerance electrocardiogram was taken. Electrocardiograms were performed in this manner so as not to miss any of those rare patients in whom smoking causes a recurrence of chest pain, recently induced by exercise, and also patients in whom, immediately after smoking, pain and electrocardiographic changes on exertion are more severe.

By this manner of investigation, only 3 patients showed electrocardiographic changes appearing after smoking and exercise. The incidence of chest pain precipitated by smoking was 6% (20 out of 309 cases); only 1% showed electrocardiographic signs of myocardial ischemia during smoking.

b. Electrocardiogram of non-anginal subjects. In healthy subjects the examination of the electrocardiogram of smokers failed to show a significant difference in frequency of the ischemic pattern in the electrocardiogram as compared with that of nonsmokers.[36-40] In similar surveys by other investigators, there were more smokers in the group that showed ischemic response in the electrocardiogram during exercise. Doyle and Kingh[41] reported that 69% of subjects giving an ischemic response were smokers, whereas, 37% of those with a normal electrocardiogram were smokers. Kattus et al.[42] obtained the

1005105295

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

respective incidence of 59% and 42%. As in other studies, the role of various risk factors could not be excluded. When the heart was stressed by hypoxia, there was no difference between smokers and nonsmokers in the T-area vectors of the electrocardiogram.[43] The QRS complex showed a right axis deviation in some smokers.[44] The polarcardiogram, which graphs the polar coordinates of the heart vectors vs. time, indicates a difference between smokers and nonsmokers.[45] The complexity of the technique prevents its widespread application to determine the significance of the difference.

3. Coronary Arteriography.

The effect on the coronary arteries of the smoking of cigarettes has been investigated in man by arteriography. Likoff et al.[46] tested the smoking of 2 cigarettes in each of 10 patients with coronary heart disease. No effect on the size of the vessels was observed by cineradiography.

The results of coronary arteriography in patients with angina pectoris did not show a relationship consistent with the amount of cigarette smoking. Newton et al.[47] examined 80 patients with angina pectoris and made the following observations:

43 normal arteriograms: 29 subjects were smokers.

46 abnormal arteriograms: 40 subjects were smokers.

They concluded that smoking was not related to the anatomical findings at

1005105296

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

coronary arteriography.

Banks et al.[48] examined 107 patients with ischemic heart disease (66%) and nonischemic heart disease (28%), most of the latter with rheumatic heart disease:

68 cases of ischemic heart disease: 39 subjects were smokers.

39 cases of nonischemic heart disease: 14 subjects were smokers.

The arteriogram was scored according to the degree of obstruction of all three coronary arteries. There was no correlation between the number of cigarettes smoked and the extent of disease in any of the arteries. Even the total coronary arterial score did not bear any significant relation to the tobacco consumption. There is, therefore, no indication by arteriography that cigarette smoking produces obstructive lesions in patients with heart disease, nor does smoking exert any coronary vasospasm.

4. Does Carbon Monoxide Provoke Angina Pectoris?

A review of the literature indicates that there is no definitive evidence to support the contention that the carbon monoxide present in cigarette smoke provokes angina pectoris in patients suffering from this disease. The widely-quoted studies of Aronow and his collaborators show a reduction in exercise performance when anginal patients either smoke cigarettes or inhale atmosphere containing carbon monoxide. The uniformity of the results derived from groups of 8 or 10 patients questions the validity of the techniques used and suggests the uniqueness of the patients used for the study. In a survey of 309 patients with

1005105297

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

objective recording of the electrocardiogram, only three patients showed a reduction in exercise tolerance judged by ischemic pattern of the electrocardiogram in the course of smoking cigarettes.

Tolerance to exercise was originally used for diagnosis of coronary heart disease, and not for evaluating a deterioration of the patient, such as by inhaling carbon monoxide. There have been no prospective studies showing that anginal patients who experience a reduction in exercise performance die sooner from myocardial infarction than those patients whose exercise performance improves. There is evidence to the contrary relating to patients who develop myocardial infarction (see section B).

In healthy adults, tolerance to vigorous exercise to the point of exhaustion is sometimes reduced in smokers compared to nonsmokers.[49-53] These reports are based on a limited number (10 to 20) of subjects. In larger prospective studies, cigarette smoking did not reduce the capacity to exercise. Morris et al. reported that smokers could tolerate vigorous exercise as well as nonsmokers among 16,882 office workers.[54] Cyntelberg showed that smokers had significantly higher physical fitness than nonsmokers in a group of 5,249 middle-aged Danish male workers.[55] In a group of 78 American male faculty members, Coleman et al. reported no difference in the aerobic capacity scores or physical work capacity between smokers and nonsmokers.[56] These observations indicate that measurements of tolerance to vigorous exercise on a treadmill or a bicycle ergometer to the point

1005105298

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

of exhaustion are not relevant to ordinary exercise and to occupational performance (see Chapter 7). A similar question can be raised in the evaluation of anginal patients by means of a treadmill which is a more vigorous form of exercise than any activity patients are ordinarily exposed to in their daily living.

B. Myocardial Infarction

The literature on myocardial infarction is almost entirely epidemiologic in nature. It has been suggested that the carbon monoxide contained in cigarette smoke is a major factor in the occurrence of myocardial infarction among cigarette smokers. An examination of relevant publications does not support this contention.

1. Association Between Atherosclerotic Disease and Carbon Monoxide Exposure.

The cross-sectional study of Wald et al.[57] on 1,085 volunteers who worked for several firms in Copenhagen is usually cited to support the hypothesis that elevation of carboxyhemoglobin levels in tobacco smokers is associated with a high incidence of atherosclerotic disease. It should be stated at the outset that the epidemiologic study consisted entirely of Danish smokers and there were no nonsmokers for comparison. There was actually no relationship between the smoking history and the incidence of ischemic heart disease. However, the carboxyhemoglobin levels in smokers were found to provide a better

1005105299

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

indication of the person's risk of developing atherosclerotic diseases.

The above results can be interpreted to signify that sources of carbon monoxide, other than cigarette smoke relate to the incidence of disease, rather than smoking per se. This possibility was not considered by Wald et al.[57] Instead, Wald et al.[58] described a method of evaluating exposure of smokers by combining carboxyhemoglobin measurement, the smoking history and the carbon monoxide yield produced by each cigarette. The indices of tobacco smoke absorption are based on the premise that there is a build up of carboxyhemoglobin during the day in cigarette smokers.[59] However, this method proposed by Wald et al.[57] is in question because Castleden and Cole[60] failed to show an increase in carboxyhemoglobin level during the day. In a recent review of the literature, Wald and Howard[61] reiterated their earlier conclusion that carboxyhemoglobin level is correlated with the prevalence of arterial disease, independently of the amount smoked.

In all the publications by Wald, there is no mention of a 1973 article by Rea et al.[62] who performed a community study of cardiorespiratory disease in Great Britain in a group of 783 adults which included smokers and non-smokers. Although the level of carbon monoxide in the expired air correlated with the amount of cigarettes smoked, there was no correlation between carbon monoxide level and the symptoms of ischemic heart disease. This study is an important one because it is the only one published that examines carbon

10051053300

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

monoxide exposure and incidence of heart disease in smokers and nonsmokers.

2. Association Between Carboxyhemoglobin Levels and Myocardial Infarction.

In the Los Angeles area, Cohen et al.[63] studied the case fatality rates for patients admitted to hospitals with myocardial infarction. The results indicate that there is an increased fatality rise in high pollution areas during periods of relatively increased carbon monoxide pollution. These observations prompted Haywood et al.[64] to design a study at the Los Angeles County Medical Center. In 34 infarction patients and 35 control patients, there was no difference in carboxyhemoglobin level although there was a higher percentage of smokers in the infarction group.

Kuller et al.[65,66] concluded a study of the relationship between carbon monoxide exposure and heart attacks in the city of Baltimore. Unlike the results in Los Angeles, there was no correlation between the number of cases per day and the ambient carbon monoxide levels. Postmortem carboxyhemoglobin levels were slightly higher in arteriosclerotic heart disease deaths than in sudden deaths due to other causes, the higher levels appearing in smokers.

The above observations indicate that the incidence of myocardial infarction is not correlated with carbon monoxide exposure. That there are more smokers among fatalities does not mean that smoking is the cause. An examination of results of retrospective and prospective studies does not support a cause and effect relationship between smoking and myocardial infarction.

1005105301

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

a. Retrospective studies of myocardial infarction deaths. Spain et al.[67] examined a group of 102 men who died suddenly of acute myocardial infarction. The average age at the time of death was 16 years less in those who smoked heavily than it was in the nonsmokers. Porsteinsson et al.[68] reviewed a group of 119 men and 32 women who died of myocardial infarction. The average age at the time of infarction was 57.9 for smokers, 62.1 for exsmokers and 69.2 for nonsmokers. Spain et al.[67] have discussed two explanations for the occurrence of sudden death among smokers at a younger age than among nonsmokers. They discounted alteration in coagulability of the blood by smoking on the basis that the incidence of recent coronary arterial thrombi was not correlated with smoking habits. They favor the explanation that smokers as a group are, in many respects, different types of individuals from nonsmokers. This is supported in their study by the fact that the average age at which those who smoked heavily were involved in and died on account of accidents, suicide and homicide was 9 years less than the average age at which nonsmokers died because of similar events.

Survival time. Spain[69] and Spain and Bradess[70] examined 88 autopsy cases of sudden death following acute infarction. Their results were as follows:

1005105302

number of autopsy cases		(Survival rate)
18 nonsmokers:	12 survived < 1 hour and 6 survived > 8 hours	(33.3%)
30 smokers (<1 pack):	22 survived < 1 hour and 8 survived > 8 hours	(26.6%)
40 smokers (>1 pack):	38 survived < 1 hour and 2 survived > 8 hours	(5.0%)

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

Survival time was decreased in the heavier smokers. The association was less evident within the older age brackets and more striking under the age of 50.

Paras Chavero et al.[71,72] reported 106 men who had myocardial infarction. The mortality during the acute episode was as follows:

14 nonsmokers:	2 deaths (14.0%)
10 smokers (<1 pack):	1 death (5.5%)
68 smokers (> 1 pack):	11 deaths (16.2%)

Smokers consuming less than one pack daily have a lower incidence of sudden death than nonsmokers.

b. Prospective studies of patients with myocardial infarction. Although there are more cigarette smokers in patients who suffer myocardial infarction than in control groups, there is no evidence that the smokers have a more severe form of the disease. An examination of prospective studies of patients who have suffered from myocardial infarction question a cause and effect relationship between smoking and coronary arterial disease.

Patients who survive the first 24 hours after acute myocardial infarction have been examined to determine whether cigarette smoking influenced their prognosis. The conclusion has been uniformly negative. Cole et al.[73] examined 285 patients. Statistics of smoking habits were obtained for nonsmokers and smokers respectively, as follows:

1005105303

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

17 nonsmokers	29.4% died within 2 months	29.4% lived over 10 yrs
31 smokers (<1 pack)	9.6% died within 2 months	41.9% lived over 10 yrs
21 smokers (>1 pack)	14.3% died within 2 months	57.0% lived over 10 yrs

The above results show that nonsmokers did not have a better prognosis than smokers. In fact, the contrary is suggested, namely, among those who develop myocardial infarction, smokers are more apt to live longer than nonsmokers.

The duration of survival of patients following an acute myocardial infarction has been examined by other groups. The Coronary Drug Project Research Group[74] studied a total of 2,181 men. There was no association between smoking and prognosis. De Soldati et al.[75] examined 66 cases of acute myocardial infarction and noted the following mean duration of survival:

	17 nonsmokers	44.5 months
49	smokers (<1 pack)	99.6 months
	smokers (>1 pack)	56.7 months

The differences between groups were statistically significant. It can be noted that the duration of survival of [illegible] smokers is longer than that of nonsmokers.

The electrocardiograms of 175 men who survived a year without recurrence after a first myocardial infarct were examined for periods ranging from 1 to 4 years.[76] In the absence of recurrence, 10.9% at the end of 1 year and 20.0% at the end of 4 years had a normal electrocardiogram. There was no relation

1005105304

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

between the return to normal and the extent of smoking after infarction.

The electrocardiogram reflects the severity of infarction and this, in turn, influences the prognosis. Royston[77] examined at autopsy the severity of infarction of 200 hearts. The extent of damage was graded in increasing order of I, II and III. The results of that author based on smoking habits that were known for 156 cases were as follows:

32 nonsmokers:	I 54%	II 42%	III 4%
23 smokers (light)	I 52%	II 43%	III 5%
68 smokers (moderate):	I 62%	II 35%	III 3%
33 smokers (heavy):	I 61%	II 39%	III 0%

The severity of the infarct did not appear to be affected by the smoking habits.

In a study of 400 patients with myocardial infarction, Helmers[78] found no significant difference between the percentage of smokers and nonsmokers among survivors studied the first 23 hours, from 2 days until discharge, and from discharge to 3 years. Reynertson and Tzagournis[79] in a five-year prospective study of 135 patients, were also unable to find any relationship between coronary heart disease mortality rates and smoking habits prior to or after infarction.

3. What is the Significance of Carboxyhemoglobin Levels in Patients with Myocardial Infarction?

A review of the literature on myocardial infarction indicates that the carboxyhemoglobin levels in patients with myocardial infarction is an incidental finding. Some epidemiologic studies indicate a correlation between incidence of myo-

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

cardial infarction and carboxyhemoglobin levels whereas others do not support a concurrence. That majority of patients happens to be cigarette smokers may be explained by the genetic or constitutional hypothesis originally suggested by Fisher in 1959, i.e. individuals are born with a genetic make up that is responsible for the acquisition of the smoking habit and also predisposes them to developing coronary heart disease.[80] The twin registry has been established in Sweden and has afforded an opportunity to examine the role of a genetic factor in predisposing a person to smoking and to diseases. A comparison between the smoking habits of 59 pairs of adult monozygotic twins and 59 pairs of adult dizygotic twins showed a significantly-greater concordance within the monozygotic pairs.[81] These results indicate the importance of the genotype in regard to acquisition of the smoking habit.

The relation of heredity to coronary heart disease in 193 twins was examined by Lundman.[82] The series was small, so that it was impossible to draw definitive conclusions regarding heredity and the disease. In a larger series of 9,168 twin pairs, the studies of a population of first-born twins revealed an increased incidence of angina among male smokers in urbanized areas that was 1.50 times that of smokers in rural districts. No difference between areas was found with respect to nonsmokers; therefore, the combination of smoking and the urban factor seems to be associated with the symptom of angina. Since there was no difference in incidence of angina in smoking discordant-twin pairs, it is unlikely that there is a causal relationship.[83-85] There was a

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

higher concordance rate among monozygotic twin pairs with regard to angina pectoris than among dizygotic twin pairs, which suggests the existence of a genetic predisposition for the development of coronary heart disease.[86]

Additional data from the Swedish twin study has been reported by Friberg et al.[87] They found an excess coronary heart disease mortality among smokers in dizygotic twins with different degrees of smoking, but no excess in monozygotic twins. The authors suggest that these results support the theory originally proposed by Fisher[80] that predisposition to smoking and to coronary heart disease may be caused by a common genotype.

C. Cardiac Effects of Carbon Monoxide, Nicotine and Cigarette Smoke

Thus far, this chapter has been devoted entirely to the investigation of the effects of carbon monoxide and cigarette smoke in patients with angina pectoris or myocardial infarction. The supposition that carbon monoxide contained in cigarettc smoke provokes an anginal attack and causes acute myocardial infarction is based not only on the material already covered (A and B) but on additional misconceptions derived from interpretation of results from human and animal experimentation. The effects of carbon monoxide are equated with those of cigarette smoke, although the latter also contains nicotine. This section reviews the pharmacologic actions of carbon monoxide separately

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

from nicotine to arrive at the combined action of cigarette smoke.

1. Carbon Monoxide.

In human cases of carbon monoxide poisoning, there are abnormalities in the electrocardiogram indicating myocardial ischemia. These appear when carboxyhemoglobin levels exceed 50% which is high enough to produce loss of consciousness.

In dogs, the threshold saturations that produce cardiac changes were determined by Ehrich et al.[88] There was depression of the R-T segment and degenerative changes appeared at 40% carboxyhemoglobin lasting for a few hours. Heart block and myocardial hemorrhages and necroses were observed only when the carboxyhemoglobin level exceeded 75% for one hour or longer. In rats poisoned with 10,000 ppm carbon monoxide inhalation for 10 min, high enough to elevate carboxyhemoglobin to 65%, ultrastructural changes in the heart, consisting of intracellular edema, swelling of mitochondria and disruption of lysosomes, were reported. Suzuki[89] concluded that the effects of carbon monoxide on the heart result not only from hypoxemia but also from the direct toxic effects on the specific respiratory enzymes. In 24 hours after the inhalation, the hearts of most rats appeared essentially normal so that the toxic effect was reversible.

There has been no report of cardiac arrhythmia in cases of carbon monoxide poisoning with carboxyhemoglobin less than 20,000 ppm. In anesthetized dogs, Kaul et al.[90] failed to note any electrocardiographic changes at 20 to 35%,

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

carboxyhemoglobin and there was no increase in vulnerability of the ventricles to hydrocarbon-epinephrine arrhythmia or to digitalis-induced fibrillation.

Levels below 20% carboxyhemoglobin in the anesthetized dog caused an increase in cardiac output and in coronary blood flow.[91-93] The threshold for the increase in cardiac output is about 10% carboxyhemoglobin and disappears at 20%.[94] The increase in coronary blood flow occurs linearly between 4 and 20% carboxyhemoglobin.[95] Myocardial contractility is increased at 5% carboxyhemoglobin to about the same extent as that during inhalation of low oxygen. The increase in contractility appears even up to 15% carboxyhemoglobin saturation.[96]

The above results are derived from animal experiments, some with open chest and the heart depressed by the use of general anesthesia. Yet, there is no sign of cardiac depression. There are no corresponding observations on the acute effects of carbon monoxide on the ischemic heart to determine whether there is any change in response.

2. Nicotine.

The effects of nicotine can be readily demonstrated in animals and human subjects. Since nicotine is primarily a cardiac stimulant, it has been suggested that the alkaloid would provoke angina and trigger acute myocardial infarction.

a. Myocardial contractility and cardiac output. The intravenous injection of nicotine causes an increase in myocardial contractility and cardiac output.

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

The mode of action has been established as due to stimulation of nicotinic receptors in the sympathetic ganglia, in the heart muscle and in the adrenal medulla.[97] The release of catecholamines from the heart is suspected of being harmful because of the increase in oxygen consumption of the heart and the ultimate depletion of the amines leading to failure of cardiac function.

There are several weaknesses in the hypothesis that nicotine by its action on the heart muscle would cause acute myocardial infarction in the tobacco smoker. The amount of nicotine absorbed during smoking is considerably less than the dose injected to elicit cardiac stimulation. It is difficult to sustain an increase in nicotine level in the blood because this alkaloid is readily metabolized after absorportion from cigarette smoke.

Frankl et al.[98] showed that smoking of cigarettes does not increase the cardiac output of patients who are predisposed to infarction. Furthermore, the release of catecholamines by nicotine does not lead to depletion. In the guinea pig heart subjected to chronic nicotine administration, there was an increase in synthesis of norepinephrine, the transmitter substance.[99] In the rabbit heart, nicotine causes the release of prostaglandin E which, in turn, would inhibit the release of norepinephrine.[100] These recent results suggest a new mechanism by which nicotine can elicit "autoinhibition" of the primary release of norepinephrine.

1005105310

b. Coronary circulation. Although the early observations that nicotine causes coronary vasospasm in the perfused isolated heart have been disproven by subsequent experimentation, some authorities continue to characterize

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

nicotine as producing coronary insufficiency. Bing and his collaborators have used several techniques to show that there is no reduction in coronary blood flow and that there was a significant correlation between supply and demand of oxygen of the canine and feline hearts following the administration of nicotine.[101-104] There is, therefore, no experimental proof to suggest that nicotine causes coronary insufficiency.

3. Cigarette Smoke.

When carbon monoxide and nicotine are absorbed in the lungs in the course of smoking cigarettes, there is reason to expect an interaction between the pharmacologic actions of the alkaloid and the gas. There are no specific observations of interaction in man, except to recall that cigarette smoking in a patient with heart disease causes either an increase of cardiac output if low, or a decrease if output is high, prior to smoking. When Gould et al.[105] described these effects, they could not offer an explanation because nicotine was known to be a depressant. It appears that a patient with heart disease and abnormal cardiac output responds in the direction to normalize cardiac output.

One suggestion for the correction of an abnormal cardiac output brought about by smoking is to consider the possibility that the multiple actions of nicotine on the heart are antagonistic. If the heart has an abnormal rhythm due to abnormalities in conduction, nicotine would facilitate conduction as reported by Bekheit and Fletcher,[106] whereas, carbon monoxide would slow

1005105311

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

conduction, a manifestation of excessive carboxyhemoglobin.[107-109] In the isolated perfused heart, Procita and Ingenito[110] could also demonstrate a depressant effect of carbon monoxide overcome by the stimulant action of nicotine. The observations of Uebekk and Mjos[111-113] that experimental ischemia of the dog heart is exaggerated by nicotine by increasing the myocardial uptake of free fatty acid should be extended to test whether carbon monoxide would prevent this metabolic action of nicotine. This possibility is not a remote one because there are observations that metabolism of free fatty acid by blood vessels is influenced by carbon monoxide, as described in the next section.

D. Experimental Atherosclerosis

The statement that carbon monoxide contained in cigarette smoke causes atherosclerosis is based on the experiments performed by Astrup, Kjeldsen and their collaborators.[114-123] An examination of the 38 articles published by them from 1967 to 1975 indicate that their experiments did not involve inhalation of cigarette smoke but of carbon monoxide in rabbits[124-134] and in human subjects. Atherosclerosis could not be demonstrated in man but was demonstrated only in rabbits that were fed a high cholesterol diet and in castrated male rabbits.[135-151] In their review articles, Astrup and Kjeldsen have transposed their results on carbon monoxide inhalation to cigarette smoking failing to mention that almost all attempts by

1005105312

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

other investigators have failed to induce atherosclerosis in animals exposed to carbon monoxide or cigarette smoke inhalation, or to nicotine injection.

This section reviews the experimental investigation according to animal species. The positive results of experimental investigation by Astrup and Kjeldsen and their collaborators are discussed together with the contradictory results of others.

1. Rabbits.

Although there are ten articles by Astrup, Kjeldsen and their collaborators on experimental atherosclerosis in the rabbit, there appears to be some repetition in that the same group of rabbits are described in two or more publications. There are three types of exposures with the following experimental observations:

Procedure	COHb Saturation	
rabbits fed with cholesterol	15 to 20% for 5 weeks	heart displayed focal degenerative changes and scattered hemorrhages[114]
		atherosclerotic lesions and changes in lactate dehydrogenase patterns in aortic arch[115]
rabbits, male and castrated	11% for 3 months	focal degenerative changes in vascular intima and heart[119]
	16-18% for 2 weeks	ultrastructural intimal changes[120] and myocardial changes[122]

100510513

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

In addition to the above, there are single exposures to 180 ppm carbon monoxide lasting for four hours producing microscopic lesions in the aortic intima and the heart.[121, 123]

The above experiments are the basis for the repeated statements by Astrup and Kjeldsen that low levels of carbon monoxide produce lesions in the heart and aorta. The lesions were seen by visual inspection only in the cholesterol-fed rabbits. The changes seen in non-cholesterol-fed rabbits were seen only under the light or electron microscope. There is a conspicuous absence of measurements of cardiac function, aortic blood pressure and organ blood flow to determine if the observed histological changes are disease processes or simply experimental artefacts that are of transient nature.

Other investigators have failed to notice any histopathological or functional changes in rabbits exposed to carbon monoxide in levels even exceeding the concentration used by Astrup, Kjeldsen and coworkers. Truhaut et al.[152, 153] did not find any alterations in the electrocardiogram or in blood pressure after 3 months exposure to 250 ppm of carbon monoxide. Andersson did not observe any change in the electrocardiogram in rabbits exposed for 14 months to carboxy-hemoglobin levels ranging from 15 to 40%.[154] Birnstingl et al.[155, 156] reported aortic lesions only if rabbits were fed with cholesterol and when exposed to carboxyhemoglobin levels of 18 to 25% for 6 months.

1005105314

Although injections of nicotine cause elevation of free fatty acid levels in the blood of rabbits,[157] the experiments that relate directly to cigarette smoke

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

do not show the development of atherosclerosis. Fisher et al.[158] exposed rabbits to cigarette smoke, daily for 11 to 13 months. The exposure failed to affect quantitatively or qualitatively atherosclerosis of the aorta, and coronary arteries, even in cholesterol-fed rabbits. The coronary angiograms were not influenced in rabbits exposed to cigarette smoke. The results of Fisher are significant in that they exclude any role of carbon monoxide in cigarette smoke in the pathogenesis of experimental atherosclerosis.

2. Mice, Rats, Hamsters and Dogs.

Chronic exposure in a chamber to low levels of carbon monoxide does not cause atherosclerosis in mice[159-162] and rats.[163-172] In the latter species, although nicotine administration[173,174] or cigarette inhalation[175] decreases lipoprotein lipase and elevates free fatty acid in the blood, arterial lesions could not be demonstrated. In hamsters, chronic inhalation of cigarette smoke did not produce vascular lesions morphologically comparable to human atherosclerosis.[176,177] Wehner et al.[178] observed that smoke-exposed hamsters lived significantly longer than sham-exposed controls. They explained their results by proposing that cigarette smoke retards amyloidosis which is a frequent cause of death in hamsters.

Dogs chronically exposed to carbon monoxide do not develop atherosclerosis.[179-181] Ahmed et al.[182] exposed one-year old beagles to either cigarette smoke inhalation or nicotine injection. After a period of two years, cardiac function was measured. There were no significant differences in left ventri-

1005105315

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

cular function and in volume. Coronary arterial obstructive disease was absent on gross and microscopic examination. The experiments in dogs have excluded the possibility that carbon monoxide and nicotine contained in cigarette smoke can induce coronary lesions and ventricular malfunction in the dogs.

3. Subhuman Primates.

Thomsen,[183] from Astrup's laboratories, exposed Macaca irus monkeys continuously (24 hours daily) to 250 ppm of carbon monoxide with mean carboxyhemoglobin values of 20.6%. After two weeks of continuous exposure, the monkeys were sacrificed without any measurements of cardiac function. The examination of the coronary arteries showed flattening of the endothelial and subendothelial spaces which Thomsen interpreted as the initiating lesion in the development of atherosclerotic vascular disease. It is this experiment that Astrup and Kjeldsen cite as evidence that carbon monoxide contained in cigarette smoke promotes the development of atherosclerosis in man.

One observation by Thomsen[183] questions the relevance of continuous carbon monoxide inhalation to cigarette smoking. Monkeys that were exposed intermittently (12 hours on and 12 hours off) did not show vascular intimal lesions. Since smoking simulates the intermittent situation, it is not justified to transpose the results of continuous carbon monoxide to the human situation.

There are two other groups of investigators who reported a positive role of chronic exposure to carbon monoxide in the pathogenesis of atherosclerosis.

1005105316

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

Webster and Clarkson[184] used squirrel monkeys fed with cholesterol and De Bias et al.[186-190] used cynomolgus monkeys exposed continuously, 23 hours daily. The criticism raised above applies to these experiments, i.e. the irrelevance of continuous exposure to the smoking situation and the fact that cholesterol-fed animals behave differently from those that are not cholesterol-fed. In any event, low levels of carbon monoxide can be excluded as causing atherosclerosis on the basis of the following: Eckardt et al.[185] exposed cynomolgus monkeys 24 hours daily for two years to carboxyhemoglobin levels of 6 to 8%. These elevated levels did not lead to cardiac fibrosis, vascular lesions and brain pathology after two years of exposure, a period considerably longer than the 6 months used by De Bias et al.,[188] 7 months by Webster and Clarkson[184] and two weeks by Thomsen.[183] If all these results are interrelated, it appears that, in subhuman primates, continuous exposure to low levels of carbon monoxide produces changes in the blood vessels initially which disappear after one or two years or less.

The fundamental question as to the role of carbon monoxide in cigarette smoke can be answered as follows: In subhuman primates, the vascular effects of continuous exposure to carbon monoxide disappear after several months, and are absent during intermittent exposures. Although nicotine alone can cause experimental deposition of triglycerides in isolated arteries,[191, 192] experiments in vivo do not show experimental atherosclerosis by injection of nicotine alone.[193]

1005105312

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

4. Human Subjects.

The colleagues of Astrup have supplied the following observations in man to support his thesis that carbon monoxide causes atherosclerosis. Exposure to carbon monoxide increases the rate of transcapillary escape of albumin[194] and decreases the oxygen affinity of hemoglobin.[195] The relevance of these observations to atherosclerosis is based on several assumptions which have been disproven in man. First, the effects of carbon monoxide on the blood are not necessarily the same as those of cigarette smoking, for instance, on the fibrinolytic activity of whole blood, platelet adhesiveness and lipolysis.[196, 199, 200] Secondly, in the perfused human coronary artery, carbon monoxide did not influence cholesterol synthesis although it increased cholesterol uptake, whereas, nicotine increased synthesis but not the uptake.[197, 198] These observations show the difference between nicotine and carbon monoxide and raise the possibility that the two together may interact, nicotine blocking the effect of carbon monoxide on the uptake, and carbon monoxide blocking the effect of nicotine on synthesis of cholesterol. If this interaction occurs in vivo, then a combination of nicotine and carbon monoxide in the proper proportion would be expected to have no effect on cholesterol deposition in the vessel wall.

10051053 18

E. Design of Future Experiments

This section has reviewed the investigations in man and animals that have been used to support the hypothesis that carboxyhemoglobin levels in cigarette smokers are high enough to cause coronary heart disease. The limitations of

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

the experimental observations are discussed above and can be summarized as follows: The results are based on the inhalation of carbon monoxide which is administered either at low levels continuously, or at high levels for brief periods. Most experiments consist of carbon monoxide administration alone. In the few experimental observations that either nicotine or cigarette smoking per se has been used, the results are different from those of carbon monoxide alone.

In the future, it is necessary to realize the shortcomings of the experimental observations that have thus far been reported to examine the cardiovascular effects of carbon monoxide contained in cigarette smoke. If at all possible, the design of investigation must include an attempt to vary the carboxyhemoglobin level associated with cigarette smoking. This is difficult to execute because smokers maintain a constant level of carboxyhemoglobin regardless of the concentration of carbon monoxide in the cigarette smoke (Chapter 2).

It could be done.

1005105816

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

BIBLIOGRAPHY

1. Aronow, W.S., Kaplan, M.A., and Jacob, D., A precipitating factor in angina pectoris, Ann Intern Med, 26, 529-536, 1968.

2. Aronow, W.S., and Swanson, A.J., Non-nicotinized cigarettes and angina pectoris, Ann Intern Med., 70, 1227, 1969.

3. Aronow, W.S., and Swanson, A.J., The effect of low nicotine cigarettes on angina pectoris. Ann. Intern. Med., 71, 599-601, 1969.

4. Aronow, W.S., The effect of smoking cigarettes on the apexcardiogram in coronary heart disease, Chest, 59, 365 368, 1971.

5. Aronow, W.S., and Rokaw, S.N., Carboxyhemoglobin caused by smoking non-nicotine cigarettes. Effects in angina pectoris, Circulation, 44, 782-788, 1971.

6. Aronow, W.S., Dendinger, J., and Rokaw, S.N., Heart rat and carbon monoxide level after smoking high-, low-, and non-nicotine cigarettes. A study in male patients with angina pectoris, Ann. Intern. Med., 74, 697-702, 1971.

7. Aronow, W.S., Harris, C.N., Isbell, M.W., Rokaw, S.N., and Imparato, B., Effect of freeway travel on angina pectoris, Ann. Intern. Med., 77, 669-676, 1972.

8. Aronow, W.S., and Isbell, M.W., Carbon monoxide effect on exercise-induced angina pectoris, Ann. Intern. Med., 79, 392-395, 1973.

9. Aronow, W.S., Stemmer, E.A., Isbell, M.W., Effect of carbon monoxide exposure on intermittent claudication, Circulation, 49, 415-417, 1974.

10. Aronow, W.S., Goldsmith, J.R., Kern, J.C., Cassidy, J., Nelson, W.H., Johnson, L.L., and Adams, W., Effect of smoking cigarettes on cardiovascular hemodynamics, Arch. Environ. Health, 28, 330-332, 1974.

11. Aronow, W.S., Cassidy, J., Vangrow, J.S., March, H., Kern, J.C., Goldsmith, J.R., Khemka, M., Pagano, J., and Vawter, M., Effect of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients, Circulation, 50, 340-347, 1974.

1005105320

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

12. Aronow, W.S., and Cassidy, J., Effect of marihuana and placebo-marihuana smoking on angina pectoris, N. Engl. J. Med., 291, 65-67, 1974.

13. Aronow, W.S., Cassidy, J., Effect of carbon monoxide on maximal treadmill exercise. A study in normal persons, Ann. Intern. Med., 83, 496-499, 1975.

14. Aronow, W.S., and Cassidy, J., Effect of smoking marihuana and of a high-nicotine cigarette on angina pectoris, Clin. Pharmacol. Ther., 17, 549-554, 1975.

15. Aronow, W.S., Smoking, carbon monoxide, and coronary heart disease, Circulation, 48, 1169-1172, 1973.

16. Aronow, W.S., Effects of carbon monoxide on coronary heart disease, Geriatrics, 29, 141-146, 1974.

17. Aronow, W.S., Tobacco and the heart, J. Am. Med. Assoc., 229, 1799-1800, 1974.

18. Aronow, W.S., Allen, W.H., and De Cristofaro, D., Response of patients and physicians to mass screening for coronary risk factors, Circulation, 52, 586-588, 1975.

19. Aronow, W.S., Cigarette smoking, carbon monoxide, nicotine, and coronary disease, Prev. Med., 4, 95-99, 1975.

20. Aronow, W.S., Introduction to Smoking and Cardiovascular Disease, Veterans Administration Hospital, Long Beach, California, 7pp., in press.

21. Aronow, W.S., Carbon Monoxide and Cardiovascular Disease, Veterans Administration Hospital, Long Beach, California, 13pp., in press.

22. Aronow, W.S., Effect of passive smoking on the cardiovascular and respiratory systems, Veterans Administration Hospital, Long Beach, California, 16pp., in press.

23. Theodore, J., Angina pectoris and carbon monoxide, Ann. Intern. Med., 78, 455, 1973.

1005105321

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

24. Garfein, O.B., and Dwyer, E.M., Continuation of "angina pectoris and carbon monoxide", Ann. Intern. Med., 78, 613, 1973.

25. Lescoe, R.J., Carbon monoxide and angina pectoris, Ann. Intern. Med., 81, 562-563, 1974.

26. Anderson, E.W., Andelman, R.J., Strauch, J.M., Fortuin, N.J., and Knelson, J.H., Effect of low level carbon monoxide exposure on onset and duration of angina pectoris. A study of ten patients with ischemic heart disease, Ann. Intern. Med. 79, 46-50, 1973.

27. Kattus, A.A., Coronary artery spasm: A new appraisal, Annu. Rev. Med., 27, 69-75, 1976.

28. Shephard, R.J., The influence of small doses of carbon monoxide upon heart rate, Respiration, 29, 516-521, 1972.

29. Regan, T.J., Frank, M.J., McGinty, J.F., Zobl, E., Hellems, H.K., and Bing, R.J., Myocardial response to cigarette smoking in normal subjects and patients with coronary disease, Circulation, 23, 365-369, 1961.

30. Regan, T.J., Hellems, H.K., and Bing, R.J., Effect of cigarette smoking on coronary circulation and cardiac work in patients with arteriosclerotic coronary disease, Ann. N. Y. Acad. Sci., 90, 186-189, 1960.

31. Regan, T.J., Martin, N.J., Frank, J., McGinty, J.T., Hellems, H.K., and Bing, R.J., Hemodynamic and myocardial metabolic response to cigarette smoking in normal and coronary subjects, Circulation, 22, 798-799, 1960.

32. Pentecost, B., and Shillingford, J., The acute effects of smoking on myocardial performance in patients with coronary arterial disease, Br. Heart J., 26, 422-429, 1964.

33. Summers, D.N., Richmond, S., and Wechsler, B.M., Cigarette smoke: Effects on lactate extraction in the presence of severe coronary atherosclerosis, Am. Heart J., 82, 458-467, 1971.

1005105322

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

34. Bargeron, L.M., Ehmke, D., Gonlubol, F., Castellanos, A., Siegel, A., and Bing, R.J., Effect of cigarette smoking on coronary blood flow and myocardial metabolism, Circulation, 15, 251-257, 1957.

35. Oram, S., and Sowton, E., Tobacco angina, Q. J. Med., 32, 115-143, 1963.

36. Agnese, G., and Buonvino, M., Sui rapporti tra consume di tabacco e cardiopatie ischemiche, G. Ig. Med. Prev., 5, 295-304, 1964.

37. Gelin, J., Elgrishi, I., Ducimetiere, P., and Richard, J.L., L'electrocardiogramme dans une population a haut risque, Bull. L'institut National de La Sante Et De La Recherche Medicale, 22, 279-288, 1967.

38. Hagerup, L., Tobaksrygning og koronare risiktorer, Ugeskr Laeger, 133, 1309-1313, 1971.

39. Van Buchem, F.S.P., Drion, E., Wigbout, M., Bosschieter, E., and Frima, J.R., Het voorkomen en de betekenis van extrasystolen en geleidingsstoornissen, Ned. Tijdschr. Geneeskd, 114, 281-286, 1970.

40. Von Ahn, B., En elektrokardiografisk undersokning av tobaks rokens inverken pa hjartat hos olika grader av rokare. I. Vanerokare, Sven. lak. tidn., 43, 3109-3136, 1946.

41. Doyle, J.T., and Kingh, S.H., The prognosis of an abnormal electrocardiographic stress test, Circulation, 41, 545-553, 1970.

42. Kattus, A.A., Jorgensen, C.R., Worden, R.E., and Lavaro, A.B., S-T-segment depression with near-maximal exercise in detection of preclinical coronary heart disease, Circulation, 44, 585-595, 1971.

43. Abel, H., Functional diagnosis of the heart by the spatial T-area vector, Acta Cardiol., 26, 163-172, 1971.

44. Borden, H.H., and Ibrahim, M.A., The epidemiology of the QRS axis measurement, Am. J. Public Health, 60, 722-730, 1970.

1005105323

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

45. Dower, G.E., and Osborne, J.A., Polarcardiographic study of hospital staff -- abnormalities found in smokers, J. Electrocariol., 5, 273-380, 1972.

46. Likoff, W., Kasparian, H., and Lehman, J.S., The effect of ethyl alcohol and inhaled cigarette smoke on the caliber of atherosclerotic coronary arteries as visualized by selective arteriography, Am. J. Cardiol., 13, 117, 1964.

47. Newton, R.M., Seale, D.L., O'Brien, W.M., and McGuire, L.B., Clinical correlations with coronary arteriography, Va. Med. Mon., 97, 688-692, 1970.

48. Banks, D.C., Raftery, E.B., and Oram, S., Clinical significance of the coronary arteriogram, Br. Heart J., 33, 863-870, 1971.

49. Krumholz, R.A., Chevalier, R.B., and Ross, J.C., Cardiopulmonary function in young smokers. A comparison of pulmonary function measurements and some cardiopulmonary responses to exercise between a group of young smokers and a comparable group of nonsmokers, Ann. Intern. Med., 60, 603-610, 1964.

50. Krumholz, R.A., Chevalier, R.B., and Ross, J.C., Changes in cardiopulmonary functions related to abstinence from smoking. Studies in young cigarette smokers at rest and exercise at 3 and 6 weeks of abstinence, Ann. Intern. Med., 62, 197-207, 1965.

51. Raven, P.B., Drinkwater, B.L., Horvath, S.M., Ruhling, R.O., Gliner, J.A., Sutton, J.C., and Bolduan, N.W., Age, smoking habits, heat stress, and their interactive effects with carbon monoxide and peroxyacetylnitrate on man's aerobic power, Int. J. Biometeorol., 18, 222-232, 1974.

52. Raven, P.B., Drinkwater, B.L., Ruhling, R.O., Bolduan, N., Taguchi, S., Cliner, J., and Horvath, S.M., Effect of carbon monoxide and peroxyacetyl nitrate on man's maximal aerobic capacity, J. Appl. Physiol., 36, 288-293, 1974.

53. Drinkwater, B.L., Raven, P.B., Horvath, S.M., Gliner, J.A., Ruhling, R.O., Bolduan, N.W., and Taguchi, S., Air pollution, exercise, and heat stress, Arch. Environ. Health, 28, 177-181, 1974.

10051053 24

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

54. Morris, J.N., Chave, S.P.W., Adam, C., Sirey, C., Epstein, L., and Sheenan, D.J., Vigorous exercise in leisure-time and the incidence of coronary heart-disease, Lancet, 1, 333-339, 1973.

55. Gyntelberg, F., Physical fitness and coronary heart disease in Copenhagen men aged 40-59. III. (Factors related to working capacity), Dan. Med. Bull., 21, 49-56, 1974.

56. Coleman, A.E., Burford, C.L., and Kreuzer, P., Aerobic capacity of relatively sedentary males, J. Occup. Med., 15, 628-632, 1973.

57. Wald, N., Howard, S., Smith, P.G., Kjeldsen, K., Association between atherosclerotic disease and carboxyhaemoglobin levels in tobacco smokers, Br. Med. J., 1, 761-765, 1973.

58. Wald, N., Howard, S., Smith, P.G., Bailey, A., Use of carboxy-haemoglobin levels to predict the development of diseases associated with cigarette smoking, Thorax, 30, 133-140, 1975.

59. Wald, N., and Howard, S., Variations in carboxyhaemoglobin levels in smokers, Br. Med. J., 1, 393, 1975.

60. Castleden, C.M., and Cole, P.V., Carboxyhaemoglobin levels of smokers and non-smokers working in the City of London, Br. J. Ind. Med., 32, 115-118, 1975.

61. Wald, N., and Howard, S., Smoking, carbon monoxide and arterial disease, Ann. Occup. Hyg., 18, 1-14, 1975.

62. Rea, J.N., Tyrer, P.J., Kasap, H.S., and Beresford, S.A.A., Expired air carbon monoxide, smoking and other variables. A community study, Br. J. Prev. Soc. Med., 27, 114-120, 1973.

63. Cohen, S.I., Deane, M., and Goldsmith, J.R., Carbon monoxide and survival from myocardial infarction, Arch. Environ. Health, 19, 510-517, 1969.

64. Haywood, L.F., Walberg, C.B., Kerr, F., Mohsenin, M., and Mohler, J., Carbon monoxide levels in acute myocardial infarction, J. Nat. Med. Assoc., 64, 114-146, 1972.

10051053325

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

65. Kuller, L.H., Radford, E.P., Swift, D., Perper, J.A., and Fisher, R., The Relationship Between Ambient Carbon Monoxide Levels, Postmortem Carboxyhemoglobin, Sudden Death and Myocardial Infarction, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland, 22 pp., in press.

66. Kuller, L.H., Radford, E.P., Swift, D., Perper, J.A., and Fisher, R., Carbon monoxide and heart attacks, Arch. Environ. Health, 30, 477-482, 1975.

67. Spain, D.M., Bradess, V.A., Matero, A., and Tarter, R., Sudden death due to coronary atherosclerotic heart disease. Age, smoking habits and recent thrombi, J. Am. Med. Assoc., 207, 1347-1349, 1969.

68. Porsteinsson, S.B., Hardason, P., and Samuelsson, S., 151 sjuklingur med kransaedastiflu a lyflaeknisdeild Landspitalans 1966-1968, Laeknabladid, 57, 255-275, 1971.

69. Spain, D.M., Sudden death from coronary heart disease: survival time, frequency of thrombi, and cigarette smoking, Am. J. Cardiol., 25, 129, 1970.

70. Spain, D.M. and Bradess, V.A., Sudden death from coronary heart disease. Survival time, frequency of thrombi, and cigarette smoking, Chest, 58, 107-110, 1970.

71. Paras Chavero, E., Mercado Contreras, E., and Quintero Novella, A., Tabaquismo cardiopatia coronaria. Su accion en la evolucion a largo plazo en el paciente que has padecido un infarto del miocardio, Arch. Inst. Cardiol. Mex., 40, 128-134, 1970.

72. Paras Chavero, E., Mercado, E., and Quintero, A., Simposio sobre problemas medicos orginados por el tabaquismo. II. Alteraciones cardiovasculares, Neumol. Cir. Torax Mex., 32, 15-18, 1971.

73. Cole, D.R., Singian, E.B., and Katz, L.N., The long-term prognosis following myocardial infarction, and some factors which affect it, Circulation, 9, 321-334, 1954.

10051053326

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

74. Coronary Drug Project Research Group, The coronary drug project: Relationship between coronary risk factors and prognosis for survival after recovery from previous myocardial infarction, Circulation, 40, 62-63, 1969.

75. De Soldati, L., Barbiero, O., Chutlian, A., Roman, M. I., Mattiauda, J., and Barreiro, N., Factores aterogenicos mas comunes observados en 66 casos de segundo infarto de miocardio, Prensa Med. Argent., 59, 71-74, 1972.

76. Cox, C. J. B., Return to normal of the electrocardiogram after myocardial infarction, Lancet, 1, 1194-1197, 1967.

77. Royston, G. R., Short stay hospital treatment and rapid rehabilitation of cases of myocardial infarction in a district hospital, Br. Heart J., 34, 526-532, 1972.

78. Helmers, C., Short and long-term prognostic indices in acute myocardial infarction, Acta Medica Scandinavica, Supplementum 555, 86 pages, 1974.

79. Reynertson, R. H., and Tzagournis, M., Clinical and metabolic characteristics. Effects on mortality in coronary disease, Arch. Int. Med., 132, 649-653, 1973.

80. Fisher, R. A., Smoking: The Cancer Controversy, Edinburgh, Oliver and Boyd, 1959.

81. Friberg, L., Kaij, L., Dencker, S. J., and Jonsson, E., Smoking habits of monozygotic and dizygotic twins, Br. Med. J., 1, 1090-1092, 1959.

82. Lundman, T., Smoking in relation to coronary heart disease and lung function in twins, Acta Med. Scand., 180, 1-50, 1966.

83. Cederlof, R., Urban factor and prevalence of respiratory symptoms and "angina pectoris". A study on 9,168 twin pairs with the aid of mailed questionnaires, Arch. Environ. Health, 13, 743-748, 1966.

84. Cederlof, R., Friberg, L., Jonsson, E., and Kaij, L., Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits, Arch. Environ. Health, 13, 726-737, 1966.

1005105327

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

85. Cederlof, R., Jonsson, E., and Lundman, T., On the validity of mailed questionnaires in diagnosing "angina pectoris" and "bronchitis", Arch. Environ. Health, 13, 738-742, 1966.

86. Cederlof, R., and Jonsson, E., Hereditary factors and "angina pectoris". A study on 5,877 twin-pairs with the aid of mailed questionnaires, Arch. Environ. Health, 14, 397-400, 1967.

87. Friberg, L., Cederlof, R., Lorich, U., Lundman, T., and Defaire, U., Mortaility in twins in relation to smoking habits and alcohol problems, Arch. Environ. Health, 27, 294-304, 1973.

88. Ehrich, W.E., Bellet, S., and Lewey, F.H., Cardiac changes from CO poisoning, Am. J. Med. Sci., 208, 511-523, 1944.

89. Suzuki, T., Effects of carbon monoxide inhalation on the fine structure of the rat heart muscle, Tohoka J. Exp. Med., 97, 197-211, 1969.

90. Kaul, B., Calabro, J., and Hutcheon, D.E., Effects of carbon monoxide on the vulnerability of the ventricles to drug-induced arrhythmias, J. Clin. Pharmacol., 14, 25-31, 1974.

91. Ayres, S.M., Giannelli, S. Jr., and Armstrong, R.G., Carboxyhemoglobin, hemodynamic and respiratory responses to small concentrations, Science, 149, 193-194, 1965.

92. Ayres, S.M., Mueller, H.S., Gregory, J.J., Giannelli, S., and Penny, J.L., Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHB), Arch. Environ. Health, 18, 699-709, 1969.

93. Ayres, S.M., Gianelli, S.Jr., and Mueller, H., Myocardial and systemic responses to carboxyhemoglobin, Ann. N. Y. Acad. Sci., 174, 268-293, 1970.

94. Cramlet, S.H., Erickson, H.H., Gorman, H.A., Ventricular function following acute carbon monoxide exposure, J. Appl. Physiol., 39, 482-486, 1975.

95. Adams, J.D., Erickson, H.H., and Stone, H.L., Myocardial metabolism during exposure to carbon monoxide in the conscious dog, J. Appl. Physiol., 34, 238-242, 1973.

10051105328

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

96. Scharf, S.M., Permutt, S., and Bromberger-Barnea, B., Effects of hypoxic and CO hypoxia on isolated hearts, J. Appl. Physiol., 39, 752-758, 1975.

97. Tsujimoto, A., Nishikawa, T., Dohi, T., Kojima, S., Comparison of pharmacological responses to nicotine and release of catecholamines from the adrenals in dogs and monkeys, Eur. J. Pharmacol., 26, 236-242, 1974.

98. Frankl, W.S., Winters, W.L, and Soloff, L.A., The effects of smoking on the cardiac output at rest and during exercise in patients with healed myocardial infarction, Circulation, 31, 42-44, 1964.

99. Stewart, J.E., Booker, W.M., and West, W.L., Chronic nicotine administration and norepinephrine synthesis in the isolated guinea pig heart, Arch. Int. Pharmacodyn. Therap., 201, 362-367, 1973.

100. Wennmalm, A., and Junstad, M., Nicotine mediated release of prostaglandin E from the rabbit heart, Acta Physiol. Scand., 96, 281-282, 1976.

101. Leb, G., Derntl, F., Robin, E., and Bing, R.J., The effect of nicotine on effective and total coronary blood flow in the anesthetized closed-chest dog, J. Pharmacol. Exp. Ther., 173, 138-144, 1970.

102. Bing, R.J., Wayland, H., Rickart, A., and Hellberg, K., Studies on the coronary microcirculation by direct visualization, G. Ital. Cardiol., 1, 401-408, 1971.

103. Bing, R.J., and Hellberg, K., Coronary blood flow in relation to angina pectoris, Circulation, 46, 1146-1154, 1972.

104. Tillmanns, H., Ikeda, S., Bing, R.J., The effect of nicotine on the coronary microcirculation in the cat heart, J. Clin. Pharmacol., 14, 426-433, 1974.

105. Gould, L., Venkataraman, K., Goswami, M., and Gomprecht, R.F., Cardiac effects of two cigarettes, J. Clin Pharmacol. New Drugs, 13, 76-82, 1973.

1005105329

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

106. Bekheit, S., and Fletcher, E., The effects of smoking on myocardial conduction in the human heart, Am. Heart J., 91, 712-720, 1976.

107. Seling, A., WPW-Syndrom nach akuter Intoxikation mit Kohlenmonoxyd. (Wolff-Parkinson-White syndrome following acute intoxication with carbon monoxide), Med. Klin., 61, 499-501, 1966.

108. Doumer, E., and Merlen, J.F., Syndrome de Wolff, Parkinson et White au cours d'une intoxication aigue par l'oxyde de carbone, Acta Cardiol., 1, 302-304, 1946.

109. Shafer, N., Smilary, M.G., and MacMillan, F.P., Primary myocardial disease in man resulting from acute carbon monoxide poisoning, Am. J. Med., 38, 316-320, 1965.

110. Procita, L., and Ingenito, A.J., Comparison of the cardiovascular (CV) effects of some gaseous components of tobacco smoke, Fed. Proc., 32, 805, 1973.

111. Ilebekk, A., and Mjos, O.D., Effect of nicotine on severity of acute myocardial ischemic injury in dogs, Scand. J. Clin. Lab. Invest., 33, 145-151, 1974.

112. Ilebekk, A., and Lekven, J., Cardiac effects of nicotine in dogs, Scand. J. Clin. Lab. Invest., 33, 153-159, 1974.

113. Mjös, O.D., Ilebekk, A., Effects of nicotine on myocardial metabolism and performance in dogs, Scand. J. Clin. Lab. Invest., 32, 75-80, 1973.

114. Astrup, P., Kjeldsen, K., and Wanstrup, J., Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits, J. Atheroscler. Res., 7, 343-354, 1967.

115. Hellung-Larsen, P., Laursen, T., Kjeldsen, K., and Astrup, P., Lactate dehydrogenase isoenzymes of aortic tissue in rabbits exposed to carbon monoxide, J. Altheroscler. Res., 8, 343-349, 1968.

116. Kjeldsen, K., Wanstrup, J., and Astrup, P., Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits, J. Atherosclerosis Res., 8, 835-845, 1968.

1005105330

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

117. Kjeldsen, K., Smoking and Atherosclerosis. Investigations on the Significance of the Carbon Monoxide Content in Tobacco Smoke in Atherogenesis, Copenhagen, Munksgaard, 145pp., 1969.

118. Kjeldsen, K., Astrup, P., and Wanstrup, J., Reversal of rabbit atheromatosis by hyperoxia, J. Atheroscler. Res., 10, 173-178, 1969.

119. Wanstrup, J., Kjeldsen, K., and Astrup, P., Acceleration of spontaneous intimal-subintimal changes in rabbit aorta by a prolonged moderate carbon monoxide exposure, Acta Pathol. Microbiol. Scand., 75, 353-362, 1969.

120. Kjeldsen, K., Astrup, P., and Wanstrup, J., Ultrastructural intimal changes in the rabbit aorta after a moderate carbon monoxide exposure, Atherosclerosis, 16, 67-82, 1972.

121. Thomsen, H.K., Kjeldsen, K., Threshold limit for carbon monoxide-induced myocardial damage. An electron microscopic study in rabbits, Arch. Environ. Health, 29, 73-78, 1974.

122. Kjeldsen, K., Thomsen, H.K., and Astrup, P., Effects of carbon monoxide on myocardium (ultrastructural changes in rabbits after moderate, chronic exposure), Circ. Res., 34, 339-348, 1974.

123. Thomsen, H.K., and Kjeldsen, K., Aortic intimal injury in rabbits. An evaluation of a threshold limit, Arch. Environ. Health, 30, 604-607, 1975.

124. Siggaard-Andersen, J., Kjeldsen, K., Bonde Petersen, F., and Astrup, P., A possible connection between carbon monoxide exposure, capillary filtration rate and atherosclerosis, Acta Med. Scand., 182, 397-399, 1967.

125. Astrup, P., Pauli, H.G., Kjeldsen, K., and Petersen, C.E., Introduction and general description of the study and of the procedures for prolonged exposure to carbon monoxide and hypoxia, Scand. J. Clin. Lab. Invest., 22, 5-8, 1968.

126. Kjeldsen, K., and Damgaard, F., Influence of prolonged carbon monoxide exposure and altitude hypoxia on serum lipids in man, Scand. J. Clin. Lab. Invest. 22, 10-19, 1968.

1005105331

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

127. Kjeldsen, K., and Damgaard, F., Influence of prolonged carbon monoxide exposure and high altitude on the composition of blood and urine, Scand. J. Clin. Lab. Invest., 22, 20-25, 1968.

128. Klausen, K., Rasmussen, B., Gjellerod, H., Madsen, H., and Petersen, E., Circulation, metabolism and ventilation during prolonged exposure to carbon monoxide and to high altitude, Scand. J. Clin. Lab. Invest., 22, 26-38, 1968.

129. Siggard-Andersen, J., Bonde Petersen, F., Hansen, T. I., and Mellemgaard, K., Plasma volume and vascular permeability during hypoxia and carbon monoxide exposure, Scand. J. Clin. Lab. Invest., 22, 39-48, 1968.

130. Bonde Petersen, F., Siggaard-Andersen, J., Kristensen, J. H., and Kjeldsen, K., Capillary filtration rate on the human calf during exposure to carbon monoxide and hypoxia (3454m), Scand. J. Clin. Lab. Invest., 22, 49-54, 1968.

131. Kjeldsen, K., and Mozes, M., Buerger's disease in Israel. Investigations on carboxyhemoglobin and serum cholesterol levels after smoking, Acta Chir. Scand., 135, 495-498, 1969.

132. Siggaard-Andersen, J., Petersen, F. B., Hansen, T. I., and Mellemgaard, K., Vascular permeability and plasma volume changes during hypoxia and carbon monoxide exposure, Antology, 20, 356-358, 1969.

133. Astrup, P., Intraerythrocytic 2, 3-diphospnoglycerate and carbon monoxide exposure, Ann. N. Y. Acad. Sci., 174, 252-254, 1970.

134. Astrup, P., Effects of hypoxia and of carbon monoxide exposures on experimental atherosclerosis, Ann. Int. Med., 71, 426-427, 1969.

135. Astrup, P., Kjeldsen, K., and Wanstrup, J., Effects of carbon monoxide exposure on the arterial walls, Ann. N. Y. Acad. Sci., 174, 294-300, 1970.

136. Astrup, P., Kjeldsen, K., and Wanstrup, J., The effects of exposure to carbon monoxide, hypoxia and hyperoxia on the development of experimental atheromatosis in rabbits, Atherosclerosis Proc., 2nd Int. Symposium, R. J. Jones (Editor), Chicago, Springer-Verlag, 108-111, 1970.

1005105332

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

137. Astrup, P., Karbeskadigende virkning af CO og hypoxi. (Smoking and coronary disease. Vessel injuring effect of CO and hypoxia), Lakartidningen, 67, 256-261, 1970.

138. Kjeldsen, K., Carboxyhemoglobin and serum cholesterol levels in smokers correlated to the incidence of occlusive arterial disease, Atheroscler. Proc., 2nd Int. Symposium, R. J. Jones (Editor), Springer-Verlag, New York, 378-381, 1970.

139. Kjeldsen, K., CO-eksposition og aterosclerosefrekvens. (Smoking and coronary disease. CO exposure and frequency of arteriosclerosis), Lakartidningen, 67, 262-265, 1970.

140. Astrup, P., Pathological Effects of moderate carbon monoxide exposure, Staub-Reinhaltung der Luft, 32, 20-23, 1972.

141. Astrup, P., Carbon monoxide in tobacco smoke and its influence on the development of vascular disease, Rehabilitation, 25, 11-12, 1972.

142. Astrup, P., Some physiological and pathological effects of moderate carbon monoxide exposure, Br. Med. J., 448-452, 1972.

143. Astrup, P., Carbon monoxide, smoking, and cardiovascular disease, Circulation, 48, 1167-1168, 1973.

144. Astrup, P., Carbon monoxide, smoking and atherosclerosis, Postgrad. Med. J., 49, 697-706, 1973.

145. Kjeldsen, K., Carboxyhemoglobin and serum cholesterol levels in smokers correlated to the incidence of occlusive arterial disease, Atherosclerosis Proceedings of the 2nd International Symposium, R. J. Jones (Editor), Springer-Verlag, New York, 378-381, 1970.

146. Astrup, P., and Kjeldsen, K. Carbon monoxide, smoking, and atherosclerosis, Med. Clin. North Am., 58, 323-350, 1973.

147. Astrup, P. Carbon monoxide inhalation--time for clearance from blood in reversible coma, J. Am. Med. Assoc., 230, 1064, 1974.

10051053333

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

148. Astrup, P., Pathological effects of moderate carbon monoxide exposure (Danish), Nord. Med., 89, 323, 1974.

149. Astrup, P., Carbon monoxide, smoking and cardiovascular diseases, Przeglad Lekarski, 31, 353-354, 1974.

150. Astrup, P., Kjeldsen, K., Den Humane Aterosklerose (Human Atherosclerosis), Ugeskrift for Laeger, 136, 523-531, 1974.

151. Astrup, P., Tobacco smoking and coronary disease, Acta Cardiol., 20, 105-117, 1974.

152. Truhaut, R., Boudene, C., and Claude, J.R., Sur quelques reflets humoraux de l'intoxication chronique par l'oxyde de carbone chez le Lapin. (On some humoral effects of chronic carbon monoxide poisoning in rabbits, Ann. Biol. Clin. Paris, 26, 1249-1260, 1968.

153. Truhaut, R., Boudene, C., Claude, J.R., Jacotot, B., Recnerches sur les effets de l'exposition prolongee du lapin et du rat a de tres faibles concentrations d'oxyde de carbone, III. Etude de l'action sur le systeme cardiovasculaire (1). (Research of the effects of prolonged exposure of rates and rabbats to very low concentrations of carbon monoxide. III. The effect on the cardiovascular system), Arch. Mal. Prof. Paris, 29, 189-195, 1968.

154. Andersson, A., A study of cardio-vascular alterations in animals exposed to carbon monoxide during long time, Opuscula Med., 17, 203-209, 1972.

155. Birnstingl, M., Hawkins, L., and McEwen, T., Experimental atherosclerosis during chronic exposure to carbon monoxide, Eur. Soc. Exp. Surg., 2, 92-93, 1970.

156. Birnstingl, M.A., Brinson, K., Chakrabarti, B.K., The effect of short-term exposure to carbon monoxide on platelet stickiness, Br. J. Surg., 58, 837-839, 1971.

157. Scott, R.A., Henson, D.E., Lesak, A., Turner, R.J., Malikova, S., and Hass, G.M., Relations between metabolic increase of plasma free fatty acids and the occurrence of arteriosclerotic thromboarteritis in rabbits, Am. J. Pathol., 70, 209-244, 1973.

10051053334

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

158. Fisher, E.R., Wholey, M., and Shoemaker, R., Cigarette smoking and cholesterol atherosclerosis of rabbits, Arch. Pathol., 98, 418-421, 1974.

159. Stupfel, M., Riotte, D., Roussel, A., Romary, F., Honhon, A., Girard, F., Dekov, S., Denesvre, A., Bourgeois, M., Bouley, G., Cavailles, M., and Pruliere, D., Esperimental study of the effects on mice and rats of 15 and 50 ppm of carbon monoxide exposure during periods between one and three months, (French), Bull. Inst. Nat. Sante, 23, 309-351, 1968.

160. Stupfel, M., and Bouley, G., Physiological and biochemical effects on rats and mice exposed to small concentrations of carbon monoxide for long periods, Ann. N.Y. Acad. Sci., 174, 342-368, 1970.

161. Chen, C., Okamoto, K., Naito, Hiroshi, Nakajima, Y., and Kusumoto, S., Effects - Human health: Toxicity, tissues, carbon monoxide, J. Japan Soc. Air Pollution, 5, 150, 1970.

162. MacKenzie, W.F., Patrick, R.L. Jr., and Monteleone, P.N. Jr., Pathology in animals exposed to high concentrations of carbon monoxide for six months, Proc. Conf. Environ. Toxic., 23-27, 1970.

163. Asmussen, E., and Paulsen, N.V., Cardiac hypertrophy in CO-treated young rats and their ability to withstand stress. Acta Physiol. Scand. 29, 307-313, 1953.

164. Truhaut, R., Boudene, C., and Claude, J.R., Thyroid fixation of iodine - 131 in the rat chronically poisoned with carbon monoxide, (French), Ann. Biol. Clin. Paris, 23, 73-82, 1965.

165. Ramsey, J.M., The immediate haematological response in the rat to experimental exposures of carbon monoxide, J. Physiol., 202, 297-304, 1969.

166. Mazaleski, S.C., Coleman, R.L., Duncan, R.C., and Nau, C.A., Subcellular trace metal alterations in rats exposed to 50 ppm of carbon monoxide, Am. Ind. Hyg. Assoc. J., 31, 183-188, 1970.

10051053335

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

167. Mazeleski, S. C., Effects - Human Health: Carbon monoxide, rats, toxicity, metals, Oklahoma Univ., Oklahoma City, Thesis (Ph. D.), 106pp., 1968.

168. Jones, R. A., Strickland, J. A., Stunkard, J. A., and Siegel, J., Effects of experimental animals of long-term inhalation exposure to carbon monoxide, Toxicol. Appl. Pharmacol., 19, 46-53, 1971.

169. Penney, D., Benjamin, M., and Dunham, E., Effect of carbon monoxide on cardiac weight as compared with altitude: effects, J. Appl. Physiol. 37, 80-84, 1974.

170. Penney, D., Sakai, J., and Cook, K., Health growth: Interacting effects of carbon monoxide and age, Growth, 38, 321-328, 1974.

171. Penney, D., Dunham, E., and Benjamin, M., Chronic carbon monoxide exposure: time course of hemoglobin, heart weight and lactate dehydrogenase isozyme changes, Toxicol. Appl. Pharmacol., 28, 493-497, 1974.

172. Bartlett, D., Jr., Postnatal growth of the mammalian lung: Lack of influence by carbon monoxide exposure, Respir. Physiol., 23, 343-349, 1975.

173. Mitkov, D., Milenkov, H., Kantarev, N., Influence of nicotine on the activity of lipoprotein lipase, Folia Medica, 13, 327-331, 1971.

174. Bizzi, A., Tacconi, M. T., Medea, A., Garattini, S., Some aspects of the effect of nicotine on plasma FFA and tissue triglycerides, Pharmacology, 7, 216-224, 1972.

175. Milenkov, H., Mitkov, D., Peicev, P., and Georglev, G., The effect of chronic treatment with tobacco smoke upon the lipoprotein lipase and the lipolytic activity of the arterial wall of white rats, Folia Medica, 14, 339-342, 1972.

176. Reckzeh, G., and Dontenwill, W., Effects of cigarette smoke on hamsters, Arch. Environ. Health, 20, 7-15, 1970.

177. Dontenwill, W., Chevalier, H.-J., Harke, H.-P., Lafrenz, U., Reckzeh, G., and Schneider, B., The effect of long-term cigarette smoke exposure on the cardiovascular system of Syrian golden hamsters, Virchows Arch. (Pathol. Anat.), 361, 147-162, 1973.

1005105336

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

178. Wehner, A.P., Olson, R.J., and Busch, R.H., Increased life span and decreased wight in hamsters exposed to cigarette smoke, Arch. Environ. Health, 31, 146-153, 1976.

179. Lewey, F.H., and Drabkin, D.L., Experimental chronic carbon monoxide poisoning in dogs, Am. J. Med. Sci., 208, 502-511, 1944.

180. Musselman, N.P., Groff, W.A., Yevich, P.P., Wilinski, F.T., Weeks, M.H., and Oberst, F.W., Continuous exposure of laboratory animals to a low concentration of carbon monoxide, Aerospace Med., 30, 524-529, 1959.

181. Vernot, E.H., MacKenzie, W.F., MacEwen, J.D., Monteleone, P.N., George, M.E., Chikos, P.M., Back, D.C., Thomas, A.A., and Haun, C.C., Hematological effects of long-term continuous animal exposure to carbon monoxide, Proc. Conf. Environ. Toxic, 7-22, 1970.

182. Ahmed, S.S., Moschos, C.B., Regan, T.J., and Lyons, M.M., Cardiovascular effects of chronic cigarette smoking and nicotine use in beagles, Clin. Res., 22, 255A, 1974.

183. Thomsen, H.K., Carbon monoxide-induced atherosclerosis in primates. An electron-microscopic study on the coronary arteries of Macaca Irus monkeys, Atherosclerosis, 20, 233-240, 1974.

184. Webster, W.S., Clarkson, T.B., and Lofland, H.B., Carbon monoxide-aggravated atherosclerosis in the squirrel monkey, Exp. Molecular Pathol., 13, 36-50, 1968.

185. Eckardt, R.E., Macfarland, H.N., Alarie, Y.C.E., and Busey, W.M., The biologic effect from long-term exposure of primates to carbon monoxide, Arch. Environ. Health, 25, 381-387, 1972.

186. Debias, D.A., Banerjee, C.M., Birkhead, N.C., and Friedman, M.H.F., The effects of chronic exposure to carbon monoxide (100 ppm) on the cardiovascular System of Monkeys, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PB-215,527, 46pp., 1972.

1005105332

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

187. DeBias, D.A., Birkhead, N.C., Banerjee, C.M., Kazal, L.A., Holburn, R.R., Greene, C.H., Harrer, W.V., Rosenfeld, L.M., Menduke, H., Williams, N., and Friedman, M.H.F., Int. Arch. Arbeit, 29, 253-267, 1972.

188. Debias, D.A., Banerjee, C.M., Birkhead, N.C., Harrer, W.V, and Kazal, L.A., Carbon monoxide inhalation effects following myocardial infarction in monkeys, Arch. Environ. Health, 27, 161-167, 1973.

189. Debias, D.A., Banerjee, C.M., Greene, C.H., and Scott, S.D., Effect of induced myocardial infarction and carbon monoxide on the ventricular fibrillation threshold in the monkey, Fed. Proc., 33, 344, 1974.

190. DeBias, D.A., Banerjee, C.M., Birkhead, N.C., Greene, C.H., Scott, S.D., and Harrer, W.V., Effects of carbon monoxide inhalation on ventricular fibrillation, Arch. Environ. Health, 42-46, 1976.

191. Kupke, I.R., Biosynthesis of lipids in perfused dog aorta and coronary artery. II. Incorporation of (2-^{14}C) acetate into lipids of two aortic layers and of the coronary artery under the influence of nicotine, J. Molecular and Cell. Cardiol., 4, 27-38, 1972.

192. Stefanovich, V., Usui, S., The effect of nicotine on lipid synthesis in isolated arteries, Res. Commun. Chem. Pathol. Pharmacol., 6, 993-1004, 1973.

193. Fisher, E.R., Rothstein, R., Wholey, M.H., and Nelson, R., Influence of nicotine on experimental atherosclerosis and its determinants, Arch. Pathol., 96, 298-304, 1973.

194. Parving, H.H., The effect of hypoxia and carbon monoxide exposure on plasma volume and capillary permeability to albumin, Scand. J. Clin. Lab. Invest., 30, 49-56, 1972.

195. Mulhausen, R.O., Astrup, P., Mellemgaard, K., A comparison of prolonged exposure to carbon monoxide and hypoxia in man, Scand. J. Clin. Lab. Invest., 22, 9-15, 1968.

2005053538

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000

196. El-Attar, O.A., Effect of carbon monoxide on the whole fibrinolytic activity, Industr. Med. Surg., 37, 774-777, 1968.

197. Sarma, J.S.M., Tillmanns, H., Ikeda, S., and Bing, R.J., The effect of carbon monoxide on lipid metabolism of human coronary arteries, Atherosclerosis, 22, 193-198, 1975.

198. Morita, T., Bing, R.J., Lipid metabolism in perfused human coronary arteries, Proc. Soc. Exp. Biol. Med., 140, 617-622, 1972.

199. El-Ebrashy, N., El-Ashmawy, S., and Aly, A., Effect of smoking on the index of platelet adhesiveness and blood glucose level in atherosclerotic patients, J. Egypt Med. Assoc., 50, 157-168, 1967.

200. Alvarez, J.P., Clamagirand, C.P., Alonso, J.M.A., and Martin, A.V., Action of tobacco on lipolysis and its modification by insulin, Experientia, 28, 1453-1454, 1972.

100510539

Source: https://www.industrydocuments.ucsf.edu/docs/xmmx0000